

REMARKS

With entry of this amendment, claims 24, 26-29, 31-44 and 49-52 are pending in the application. Claim 49 has been amended to correct an error made when previously amending the claim. Claims 1-23, 25, 30, 45-48 and 53-56 were previously canceled without prejudice. Applicants continue to reserve the right to pursue any cancelled subject matter of these claims in one or more related applications. All of the amendments herein are fully supported by the disclosure, and no new matter has been added to the application.

No fees are believed to be due in connection with the filing of this Amendment after Final Rejection, however, should any fees be deemed necessary, the Commissioner is hereby authorized to deduct any necessary fees from Deposit Account No. 50-1050.

I. Patentability Under 35 USC § 112

Claims 24, 26-29, 31-44 and 49-52 have been rejected under 35 USC § 112, first paragraph for alleged lack of enablement on the ground that “the specification, while being enabling for treating the diseases listed in the claims, does not reasonably provide enablement for preventing the diseases” and that “[t]he claimed methods of use are not believable.” (Office Action, page 2)

Applicants respectfully traverse the foregoing ground of rejection set forth at pp. 2-4 of the Office Action, and submit that the disclosure fully describes and enables the subject matter of claims 24, 26-29, 31-44 and 49-52.

A. The Application Provides Adequate Support for the Prevention of the Various Diseases Listed in the Claims

Claims 24, 26-29, 31-44 and 49-52 as currently written require that the indicated diseases and conditions be prevented or treated “by inhibiting dopamine reuptake.”

As previously noted by Applicants, the specification indicates that each of the diseases set forth in the claims are associated with dopamine disorders. It is specifically described in Applicant’s disclosure that Parkinson’s disease (Specification, pages 1-2, paragraph [0004]), depression (Specification, page 2, paragraph [0006]), obesity (Specification, pages 2-3, paragraph [0007]; page 4, paragraph [0010]), tic disorders (Specification, page 4, paragraph [0010]) and attention deficit disorder (Specification, page 4, paragraph [0010]) are associated with dopamine disorders. Therefore, it is not speculative that (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane can be effectively employed to treat the subject disorders, which are all described as amenable to treatment by inhibition of dopamine reuptake. In addition, the

specification refers to several published journal articles teaching that “successful inhibition of dopamine reuptake has been associated with the treatment of attention deficit disorder, depression, obesity, Parkinson’s disease, a tic disorder and an addictive disorder.” (Specification, page 24, paragraph [0096])

The specification also contains detailed, enabling support regarding how the compounds of the present invention are made and used to treat the various diseases and conditions set forth in the claims. For example, the specification contains great detail regarding the preparation (Specification, pages 7-8, paragraphs [0033]-[0035]), use (Specification, pages 8-12, paragraphs [0036]-[0054]), administration (including dosages), and formulation (Specification, pages 12-17, paragraphs [0055]-[0076]) of (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane and pharmaceutically acceptable salts thereof.

Furthermore, as discussed in detail in Section II.E hereinbelow and as previously noted by Applicants, the data set forth in Tables 1, 2 and 3 on page 23 of the specification and the experiment set forth in Attachment A of the response filed by Applicants on November 14, 2005 indicate that (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl has affinity for the dopamine uptake site as measured by binding and uptake in two different model systems.

Finally, as previously noted by Applicants, it is often the case that the same drug used to treat a particular disease or condition (eg., depression; high blood pressure) is often used to prevent the recurrence of the disease or condition. Prevention is defined in the specification as referring “to a reduction in the risk of acquiring a disorder alleviated by inhibiting dopamine reuptake or to the reduction of the risk of recurrence of the disorder once cured or restored to a normal state.” (Specification, page 9, paragraph [0037]) Applicants are entitled to the full scope of their invention, including claims directed to the “prevention” of the various diseases and conditions set forth in the claims.

In conclusion, it is clear that the specification contains enabling support for the prevention of the various diseases and conditions set forth in the claims using (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane “by inhibiting dopamine reuptake.”

B. The Office has not Met its Burden for Establishing Nonenablement

The Court of Appeals for the Federal Circuit has clearly articulated the burden which rests on the Office for establishing nonenablement:

When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why

it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. [*In re Wright*, 999 F.2d 1557, 1561-1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993), emphasis added]

Furthermore, the Federal Circuit has clearly indicated that the statements contained in a patent specification must be taken to be in compliance with the enablement requirement unless there is adequate proof to the contrary:

A specification disclosure which contains a teaching of the manner of and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enablement requirement of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. [*Fiers v. Revel*, 984 F.2d 1164, 1171-1172, 25 USPQ2d 1601, 1607 (Fed Cir. 1993), emphasis in original]

In the present case, the Office has provided no evidence to call into question the enabling support provided by Applicants. Rather, the Office simply states that “[t]he claimed methods of use are not believable.” (Office Action, p. 2) Consequently, it is clear that the Office has not established a *prima facie* case of nonenablement.

C. Conclusion

In view of the foregoing, the rejection of claims 24, 26-29, 31-44 and 49-52 under 35 USC § 112, first paragraph for failure to comply with the enablement requirement is respectfully submitted to be overcome.

II. Patentability Under 35 USC § 103

The Office continues to reject claims 24, 26-29, 31-44 and 49-52 under 35 USC § 103(a) as allegedly unpatentable over Beer et al., US 6,204,284 B1, for essentially the same reasons as set forth in the prior Office Actions issued by the Office in this case.

Applicants respectfully traverse the foregoing ground of rejection and submit that the subject matter of claims 24, 26-29, 31-44 and 49-52 is neither disclosed nor suggested by Beer et al., US 6,204,284 B1—based on the facts and reasoning set forth herein below, and as presented in the prior Amendments and Responses submitted by Applicants in this case, and in view of the entire record in this application.

A. The Disclosure of Beer et al. is Limited to Addictive Disorders

The Office continues to ignore the limited nature of the disclosure of Beer et al. As previously noted by Applicants, Beer et al. is generally directed to the treatment of addictive disorders such as chemical substance abuse using the racemic mixture of 1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane. There is no disclosure or suggestion in Beer et al. that the racemic mixture of Beer et al., nor the compounds of the present invention, can be effectively used in the treatment or prevention of attention-deficit disorder, depression, Parkinson's disease and/or tic disorders. In view of this, Beer et al. cannot render obvious claims directed to the prevention and treatment of attention-deficit disorder, depression, Parkinson's disease or tic disorders using the compounds of the present invention. Therefore, claims 31-34, 35-38, 42-44 and 49-52, which are limited to the particular indicated disorders, are clearly patentable over Beer et al.

B. The Applicable Case Law Supports the Patentability of Enantiomers of Known Compounds

It is well-established under the law that the disclosure of the racemate of a compound in the prior art does not negate the patentability of an optical isomer of the compound nor render the optical isomer of the compound obvious. For example, in the case of *In re May and Eddy*, 574 F.2d 1082, 197 USPQ 601, 607 (C.C.P.A. 1978), the court held that the nonaddictive properties of an optical isomer of an analgesic compound would have been unexpected to one skilled in the art and because of this, the optical isomer was nonobvious over its racemate and corresponding optical isomers.

More recently, in the case of *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 348 F. Supp. 2d 713 (N.D.W.V., 2004), the court held that claims directed to levofloxacin, the levorotatory [or (-)] optical isomer of the racemic compound ofloxacin, and methods of using levofloxacin to treat various diseases and conditions, were patentable over the racemic compound. In particular, the court held that the unexpected lower toxicity and higher activity of levofloxacin compared to the racemic compound rendered the levorotatory optical isomer and methods of using the levorotatory optical isomer patentable over the racemate.

In view of the foregoing, it is clear that the position taken by the Office that optical isomers of a compound are necessarily obvious over racemates of the compound is unsupportable.

C. The Case Law Cited by the Office does not Support the Obviousness of the Present Invention

The Office continues to cite the case of *In re Adamson*, 125 USPQ 233 (1960) for the proposition that the motivation required by 35 USC § 103 is present in this case since “an isomer is often more reactive than the corresponding isomer or the racemate.” (Office Action, p. 3) However, as previously and repeatedly noted by Applicants, the data set forth in the specification and in Attachment A of the Response filed by Applicants on November 14, 2005 indicates that the (-) isomer is not *more* reactive, but is in fact *less* reactive, than the racemic mixture. Therefore, *Adamson* is clearly inapplicable under the present circumstances.

Furthermore, the case of *In re Adamson* is readily distinguishable under the present circumstances. In *Adamson*, the isomer involved was about twice as active as the racemic compound with respect to spasmolytic activity. In contrast, as discussed in detail below, the isolated (-) isomer has very different binding characteristics with respect to the dopamine reuptake site of the dopamine transporter, the norepinephrine uptake site of the norepinephrine transporter and the serotonin uptake site of the serotonin transporter when compared to the racemic mixture.

Clearly, the case law cited by the Office does not support the obviousness determination made by the Office in this case.

D. The Office Routinely Issues Patents Claiming Enantiomers of Compounds and their Use

The position taken by the Office is clearly inconsistent with its well-established practice of issuing patents claiming enantiomers of previously known compounds and their use.

For example, US Patent No. 6,864,257, issued March 8, 2005, contains claims to methods of using the dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, also known by the name of zopiclone, for inducing an effect selected from the group consisting of a hypnotic effect, a sedative effect and a tranquilizing effect.

U.S. Patent No. 6,844,355, issued January 18, 2005, contains claims to isomers of quinine and quinidine and their use in treating malaria.

U.S. Patent No. 6,534,508, issued March 18, 2003, contains claims to methods of treating microbial infections using the (S) optical isomer of lomefloxacin.

U.S. Patent No. 6,495,605, issued December 17, 2002, contains claims to pharmaceutical compositions containing and methods of treating pain using the (+) optical isomer of bupropion

U.S. Patent No. 6,147,077, issued November 14, 2000, contains claims directed to pharmaceutical compositions containing and methods of treating fungal diseases using optical isomers of hydroxyitraconazole.

In view of the foregoing, it is clear that the position of the Office in refusing to allow claims directed to methods of using (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane is unwarranted.

E. The Office has Properly Issued Patents in this Series of Cases

In the Final Office Action dated January 23, 2006, the Office makes the following statement:

Applicant contends that since the instant compound was allowed in the parent case, methods of using it are allowable. This is generally true but not persuasive because the Office is not in the business of perpetuating its error. (Final Office Action, p. 5)

This disturbing comment is not only contrary to the facts in this case, it is also contrary to established law that the Office cannot continue to simply ignore.

The Office continues to disregard the fact that the (-) isomer of the present invention possesses substantially and unexpectedly different biological properties from the racemic mixture of Beer et al. In particular, as previously noted by Applicants, the data set forth in Tables 1, 2 and 3 on page 23 of the specification and the experiment set forth in Attachment A of the response filed by Applicants on November 14, 2005 clearly show that the racemic mixture and the isolated (-) isomer have very different binding profile with respect to the dopamine reuptake site of the dopamine transporter, the norepinephrine uptake site of the norepinephrine transporter and the serotonin uptake site of the serotonin transporter. In this regard, the data in Table 1 on page 23 of the specification shows that while both the racemic mixture and (-) isomer have affinity for the dopamine reuptake site of the dopamine transporter, the racemic mixture actually has a *higher* binding affinity for this site than the (-) isomer, that is, the (-) isomer is not *more* reactive, but is in fact *less* reactive, than the racemic mixture. Furthermore, the data in Tables 2 and 3 on page 23 of the specification indicates that the racemic mixture has affinity for the norepinephrine uptake site of the norepinephrine

transporter and the serotonin uptake site of the serotonin transporter, while the (-) isomer had no measurable affinity for these sites. It must be emphasized that this is not simply a case “where an isomer is expected to be more active than the racemate or the other isomer.” (Final Office Action, p. 3) Rather, in this instance, the (-) isomer has a completely different receptor binding profile when compared to the racemic mixture.

Additionally, experiments summarized in Attachment A of the Response filed by Applicants on November 14, 2005 and performed using more sensitive model systems further demonstrate the completely different receptor binding profile of the (-)-isomer of the present invention when compared with the racemic mixture of Beer et al. In these experiments, (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl, (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl and (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl were compared in dopamine, norepinephrine, and serotonin transporter binding and uptake assays using recombinant human receptors. In particular, the data in Table 1 of Attachment A referred to above indicate that the (-) isomer, the (+) isomer and the racemic mixture all have affinity for the dopamine uptake site as measured by binding and uptake. Conversely, the data in Table 1 show that the (+) isomer and the racemic mixture have substantially greater affinity for the serotonin and norepinephrine uptake sites than (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane HCl as measured by both binding and reuptake. With respect to binding to the serotonin uptake site, there is a 3.93 fold difference between the (-) isomer and the racemic mixture and a 7.47 fold difference between the (-) isomer and the (+) isomer. With respect to binding to the norepinephrine uptake site, there is a 2.72 fold difference between the (-) isomer and the racemic mixture and a 3.93 fold difference between the (-) isomer and the (+) isomer. With respect to uptake at the serotonin uptake site, there is a 9.63 fold difference between the (-) isomer and the racemic mixture and a 10.8 fold difference between the (-) isomer and the (+) isomer. With respect to uptake at the norepinephrine uptake site, there is a 5.07 fold difference between the (-) isomer and the racemic mixture and a 4.52 fold difference between the (-) isomer and the (+) isomer.

Indeed, based in part on these differences, claims directed to (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane (USPN 6,569,887) have been previously found to be patentable, as have claims directed to methods of treating or preventing disorders alleviated by inhibiting dopamine reuptake using (-)-1-(3, 4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane (USPN 6,716,868). These allowances were clearly proper and not in error, as implied by the statement quoted above that “the Office is not in the business of perpetuating its error.” (Final Office Action, p. 5)

Further, as previously noted, the position taken by the Office is inconsistent with established law. In particular, in the case of *In re Pleuddemann*, 15 USPQ2d 1738 (Fed. Cir. 1990), previously discussed in detail in the Response dated November 14, 2005 filed by Applicants, the Federal Circuit reversed a decision of the USPTO Board of Patent Appeals and Interferences, with the Federal Circuit holding that claims in a divisional case filed pursuant to a Restriction Requirement entered by the Office in the parent case and directed to methods of using compounds previously found patentable by the Office in the parent case were also patentable. This long-standing authority applies directly to the facts presented in the instant application. As a result of restriction requirements imposed by the Office, Applicants were compelled to prosecute compound claims directed to their novel (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexanes in separate applications from Applicants' novel methods of use employing these compounds. Applicants' compound claims, directed to (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexanes, have been previously examined and determined by the Office to be patentable (USPN 6,569,887). Additionally, the Office previously examined and allowed Applicants' distinct invention to generic methods of using (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane to treat disorders alleviated by inhibiting dopamine reuptake (USPN 6,716,868). Considering these antecedent dispositions by the PTO, in light of the authority presented above, Applicants are clearly entitled to additional claims employing their novel and unobvious (-)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexanes in the instantly recited methods.

F. Conclusion

In view of the foregoing, it is respectfully submitted that the rejection of claims 24, 26-29, 31-44 and 49-52 under 35 USC § 103(a) as allegedly unpatentable over Beer et al., US 6,204,284 B1 should be withdrawn.

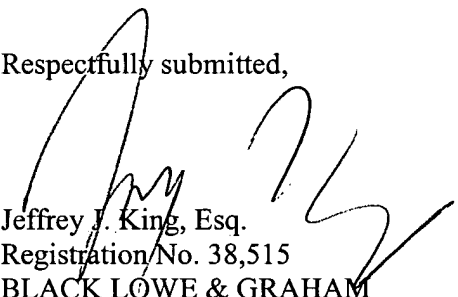
CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at (206) 381-3300.

Dated this 20th day of March, 2006.

Respectfully submitted,



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